Amendments to the Claims:

The listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

Claims 1-32 (canceled)

Claim 33 (currently amended): A method of identifying an optimal range of zeta potential for a composition for targeting to an activated vascular site comprising evaluating zeta potential of the composition for vascular endothelial cell uptake, wherein the composition is associated with different amounts of a cationic component that targets the composition to the activated vascular site and wherein the composition and the cationic components form colloids having a size of about 10 nm to about 400 nm, and identifying an optimal range of zeta potential.

Claim 34-36 (canceled)

Claim 37 (withdrawn): An imaging composition for selective targeting to an activated vascular site comprising an imaging agent obtained by the method of claim 58 and a carrier.

Claim 38 (withdrawn): The imaging composition of claim 37, wherein the imaging agent is selected from the group consisting of iron oxide particles, dyes, fluorescent dyes, NMR labels, scintigraphic labels, gold particles, PET labels, ultrasound contrast media, and CT contrast media.

Claim 39 (withdrawn): The imaging composition of claim 37, wherein the composition comprises particles having a zeta potential in the range of about +25 mV to +60 mV in about 0.05 mM KCl solution at about pH 7.5.

Claim 40 (withdrawn): The imaging composition of claim 39, wherein the composition comprises particles having a zeta potential in the range of about +30 to +50 mV in about 0.05 mM KCl solution at about pH 7.5.

Claim 41 (withdrawn): A therapeutic composition for selective targeting to an activated vascular site comprising a therapeutically effective amount of an agent obtained by the method of claim 58 and a carrier.

Claim 42 (withdrawn): The therapeutic composition of claim 41, wherein the agent is selected from the group consisting of cytostatics and cytotoxic agents.

Claim 43 (withdrawn): The therapeutic composition of claim 42, wherein the cytostatics and cytotoxic agents are selected from the group consisting of taxanes, inorganic complexes, mitose inhibitors, hormones, anthracyclines, antibodies, topoisomerase inhibitors, anti-inflammtory agents, alkaloids, interleukins, cytokines, growth factors, proteins, peptides, and tetracyclines.

Claim 44 (withdrawn): The therapeutic composition of claim 41, wherein the agent is selected from the group consisting of etherlipid, alkyllysolecithin, alkyllysophopholipid, lysolipid, alkylphospholipid.

Claim 45 (withdrawn): The therapeutic composition of claim 44, wherein the etherlipid is selected from the group consisting of 1-O-octadecyl-2-O-methyl-rac-glycero-3-phosphocholine, 1-O-Hexadecyl-2-O-methyl-sn-glycerol, Hexadecyl phosphocholine, Octadecylphosphocholine.

Claim 46 (withdrawn): The therapeutic composition of claim 41, wherein the composition comprises particles having a zeta potential in the range of about +25 mV to +60 mV in about 0.05 mM KCl solution at about pH 7.5.

Claim 47 (withdrawn): The composition of claim 46, wherein the composition comprises particles having a zeta potential in the range of about +30 to +50 mV in about 0.05 mM KCl solution at about pH 7.5.

Claim 48 (withdrawn): A therapeutic composition effective for the treatment of an angiogenesis associated disease comprising an agent obtained by the method of claim 58 and a carrier, wherein the composition further being labeled or packaged with directions for the administration of the composition to treat an angiogenesis associated disease.

Claim 49 (withdrawn): A therapeutic composition effective to inhibit inflammation comprising an agent obtained by the method of claim 58 and a carrier, wherein the composition further being labeled or packaged with directions for the administration of the composition to inhibit inflammation.

Claim 50 (withdrawn): A therapeutic composition effective to promote bone repair or wound healing, comprising an agent obtained by the method of claim 58 and a carrier, wherein the composition further being labeled or packaged with directions for the administration of the composition to promote bone repair or wound healing.

Claim 51 (withdrawn): A diagnostic composition effective for diagnosis or imaging of an angiogenesis associated disease comprising an active agent obtained by the method of claim 58 and a carrier, wherein the composition further being labeled or packaged with directions for

the administration of the composition to diagnose or image an angiogenesis associated disease.

Claim 52 (canceled)

Claim 53 (previously presented): A method of claim 33 wherein the cationic component is selected from the group consisting of:

(a) particles;

(b) liposomes comprising cationic lipids in the range of about 25 mol% to about 50 mol%; and

(c) oil-in-water emulsions or microemulsions comprising cationic amphiphiles characterized by comprising two fatty acid chains or alkyl chains in the outer layer in the range of about 25 mol% to 60 mol%.

Claim 54 (previously presented): A method of claim 53, wherein the a zeta potential is measured in about 0.05 mM KCl solution at about pH 7.5

Claim 55 (previously presented): A method of claim 33, wherein the cationic component comprises molecules having an isoelectric point above 7.5.

Claim 56 (previously presented): A method of claim 33, wherein the cationic component comprises magnetosomes with a cationic lipid layer.

Claim 57 (previously presented): A method of claim 56, wherein the zeta potential is measured in about 0.05 mM KCl solution at about pH 7.5.

Claim 58 (currently amended): A method of modifying an agent to enhance its efficacy comprising associating the agent with one or more cationic components to produce a composition having an optimal range of zeta potential for specific targeting to an activated vascular site, and dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400nm, wherein the cationic components target the composition to the activated

vascular site, and wherein the composition has a zeta potential in the range of about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 75.

Claim 59 (previously presented): A method of claim 58, wherein the cationic components are selected from the group consisting of :

(a) particles;

(b) liposomes comprising cationic lipids in the range of about 25 mol% to about 50 mol%; and

(c) oil-in-water emulsions or microemulsions comprising cationic amphiphiles characterized by comprising two fatty acid chains or alkyl chains in the outer layer in the range of about 25 mol% to 60 mol%.

Claim 60 (currently amended): A method of modifying an agent to enhance its efficacy comprising associating the agent with one or more cationic components to produce a composition having an optimal range of zeta potential for specific targeting to an activated vascular site and dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400nm, wherein the cationic components comprise molecules having an isoelectric point above 7.5 and target the composition to the activated vascular site, and wherein the composition has an isoelectric point above 7.5.

Claim 61 (previously presented): A method of modifying an agent to enhance its efficacy comprising associating the agent with one or more cationic components to produce a composition having an optimal range of zeta potential for specific targeting to an activated vascular site, wherein the cationic components comprise magnetosomes with a cationic lipid layer and target the composition to the activated vascular site, and wherein the composition has a zeta potential in the range of about +25 to +100 mV in about 0.05 mM KCl solution at about pH 7.5.

Claim 62 (previously presented): A method of claims 33, wherein the composition comprises an agent selected from the group consisting of imaging agent, therapeutic agent, and diagnostic agent.

Claim 63 (previously presented): A method of any one of claims 58, 60, or 61, wherein the agent is selected from the group consisting of imaging agent, therapeutic agent, and diagnostic agent.

Claim 64 (previously presented): A method of claim 62, wherein the imaging agent is selected from the group consisting of iron oxide particles, dyes, fluorescent dyes, NMR labels, scintigraphic labels, gold particles, PET labels, ultrasound contrast media, and CT contrast media.

Claim 65 (previously presented): A method of claim 63, wherein the imaging agent is selected from the group consisting of iron oxide particles, dyes, fluorescent dyes, NMR labels, scintigraphic labels, gold particles, PET labels, ultrasound contrast media, and CT contrast media.

Claim 66 (previously presented): A method of claim 62, wherein the therapeutic agent is selected from the group consisting of cytostatic agent and cytotoxic agents.

Claim 67 (previously presented): A method of claim 63, wherein the therapeutic agent is selected from the group consisting of cytostatic agent and cytotoxic agents.

Claim 68 (previously presented): A method of claim 66, wherein the cytostatic agent or cytotoxic agent is selected from the group consisting of taxanes, inorganic complexes, mitose inhibitors, hormones, anthracyclines, antibodies, topoisomerase inhibitors, anti-inflammtory agents, alkaloids, interleukins, cytokines, growth factors, proteins, peptides, and tetracyclines

Claim 69 (previously presented): A method of claim 67, wherein the cytostatic agent or cytotoxic agent is selected from the group consisting of taxanes, inorganic complexes, mitose inhibitors, hormones, anthracyclines, antibodies, topoisomerase inhibitors, antiinflammtory agents, alkaloids, interleukins, cytokines, growth factors, proteins, peptides, and tetracyclines.

Claim 70 (withdrawn): A method of claim 62, wherein the therapeutic agent is selected from the group consisting of etherlipid, alkyllysolecithin, alkyllysophopholipid, lysolipid, and alkylphospholipid.

Claim 71 (withdrawn): A method of claim 63, wherein the therapeutic agent is selected from the group consisting of etherlipid, alkyllysolecithin, alkyllysophopholipid, lysolipid, and alkylphospholipid.

Claim 72 (withdrawn): A method of claim 70, wherein the etherlipid is selected from the group consisting of 1-O-octadecyl-2-O-methyl-rac-glycero-3-phosphocholine, 1-O-Hexadecyl-2-O-methyl-sn-glycerol, Hexadecyl phosphocholine, and Octadecylphosphocholine.

Claim 73 (withdrawn): A method of claim 71, wherein the etherlipid is selected from the group consisting of 1-O-octadecyl-2-O-methyl-rac-glycero-3-phosphocholine, 1-O-Hexadecyl-2-O-methyl-sn-glycerol, Hexadecyl phosphocholine, and Octadecylphosphocholine.

Claim 74 (previously presented): A method of claim 58, wherein the cationic components are selected from the group consisting of DOTAP, DOPE, DOPC, iron oxide particles, and dextran.

Status of the Claims

Claims 33, 37-51, and 53-74 are currently pending in the present application. Claims 1-32, 34-36, and 52 have been canceled. Claims 37-51 and 70-73 are withdrawn from examination as being directed to a separate invention. Claims 33, 58, and 60 have been amended. Claims 33 and 53-69 and 74 are currently examined.

Amendments to the Specification and the Claims

Paragraph [0014] of the specification has been amended to correct the patent number for the referenced U.S. Patent and to correct an inadvertent grammatical error.

Claims 33, 58, and 60 have been amended to provide a specific embodiment of the invention. Support for the amendment can be found in paragraphs [0011] (line3), [0058] (line 2), [0147] (line7), and [0178] (line 14).

Rejection of the Claims Under 35 U.S.C. § 102(b)

Claim 33 is rejected under 35 U.S.C. § 102(b) as being anticipated by Watts *et al.*

As amended, claim 33 includes the limitation that the composition and the cationic components form colloids having a size of about 10nm to about 400 nm.

Applicants respectfully submit that Watts *et al.* do not teach a method of identifying an optimal range of zeta potential for a composition for targeting to an activated vascular site comprising evaluating zeta potential of the composition for vascular endothelial cell uptake and identifying an optimal range of zeta potential, wherein the composition is associated with different amounts of a cationic component and wherein the composition and the cationic component form colloids having a size of about 10 nm to 400 nm. The composition of Watts *et al.* does not meet the limitations specified for the composition and cationic components of claim 33. The cross-linked or solidified microspheres of chitosan and the active compound of Watts *et al.* have a size of about 1-200 μm or 1-100 μm. The particles in the composition of Watts *et al.* are at least twice the size of that specified in claim 33. Applicants submit that as specified in claim 33, the claimed method identifies a composition for targeting an activated vascular site and that only a small sized colloid will be able to reach the activated vascular site. As explained in

the previous Office Action, the activated vascular site is a single pavement layer of cells that line the lumenal surface of the entire vascular system and can only be targeted intravenously with small molecules of less than about 400 nm. Large microspheres, such as those of Watts will not reach the activated vascular site. Watt *et al.* do not teach a method of identifying an optimal range of zeta potential for a composition for targeting to an activated vascular site. Thus, Watts *et al.* do not anticipate claim 33.

Rejection of the Claims Under 35 U.S.C. § 103(a)

A. Claims 53-55, 58-63, and 67-69 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Watts *et al.*

Applicants respectfully point out that claims 56 and 57, which include the limitation that the cationic component comprises magnetosome are not included in this rejection. Accordingly, Applicants assume that claim 61 which also include the same limitation was inadvertently included in this rejection. Also, Watts *et al.* do not teach magnetosomes. Therefore, claim 61, like claims 56 and 57, are allowable.

Claim 33 has been amended to include the limitation that the composition and the cationic components form colloids having a size of about 10 nm to about 400 nm. Claim 58, and 60 have been amended to include the limitation that the composition forms colloids having a size of about 10 nm to about 400 nm. Claims 53-55, 59, 61-63, and 67-69 are dependent upon claim 33, 58, or 60.

As discussed under the § 102(b) rejection, the composition of Watts *et al.* do not teach the method of claim 33. Therefore, Watts *et al.* do not teach the method of the dependent claims 53-55, 62, 63, and 67-69. Moreover, Watts *et al.* do not provide motivation to modify their composition comprising particles or microspheres having a size of about 10 nm to about 400 nm because Watts *et al.* are only interested in the delivery of their composition to the mucosa, and because large microspheres of 1-200 μm or 1-100 μm are able to target the mucosa. Thus, Watts *et al.* do not render claims 53-55, 62, 63, and 67-69 obvious.

Regarding claims 58-60, Watts *et al.* do not teach a method of modifying an agent to enhance its efficacy comprising associating the agent with one or more cationic components to produce an optimal zeta potential for specific targeting to an activated vascular site, and dispersing the composition in a medium to form colloids having a size of about 10 nm to about

400 nm, wherein the composition has a zeta potential in the range of about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5, or has an isoelectric point of above 7.5. Further, Watts *et al.* do not provide motivation to modify their composition comprising particles or microspheres having a size of about 10 nm to about 400 nm because large microspheres of 1-200 μm or 1-100 μm are able to target the mucosa. Thus, Watts *et al.* do not render the claimed methods obvious.

B. Claims 64-66 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts *et al.* as applied to claims 53-55, 58-63, and 67-69 and further in view of Podolski *et al.* (WO 97/47323).

Claims 64-66 and 74 are dependent upon amended claims 33 and 58 which have been amended to include a size limitation for the colloids formed from the composition.

The deficiencies of Watts *et al.* already have been discussed above. Podolski *et al.* teach iron/chitosan/drug particles for oral delivery. Podolski *et al* do not teach a method of identifying an optimal range of zeta potential for a composition for targeting an activated vascular site or a method of modifying an agent to enhance its efficacy comprising associating the agent with one or more cationic components to produce a composition having an optimal range of zeta potential for specific targeting to an activated vascular site. Moreover, Podolski *et al.* do not teach preparing iron/chitosan/drug particles having the specific size of 10 nm to 400 nm. Rather, in Example 1, Podolski *et al.* disclose preparing iron/chitosan particles having about 2 to about 10 μm in diameter and incorporating the drug into the iron/chitosan particles for oral delivery of the drug. Podolski *et al.* acknowledges on page 4, lines 29 and 30, that larger particles are more easily tolerated in an oral system.

Although Podolski *et al.* generally discuss other methods of delivery such as intravenous and intramuscular which require smaller sized particles and Podolski *et al.* generally discuss sonicating the iron/chitosan particles to a size of less than 10 μm in diameter, preferably less than 5 μm in diameter, and until the particles are less than 5 nm in diameter, Podolski *et al.* do not specifically disclose intravenous or intramuscular drug delivery with the iron/chitosan particles and do not specifically teach dispersing the particles in a medium to form colloids having a specific size of 10 nm to 400 nm. Moreover, Podolski *et al.* do not teach delivery of their

composition to an activated vascular site. Rather, the focus of the invention of Podolski *et al.* is oral delivery to the gastro-intestinal tract, which may be accomplished with particles larger than 400 nm.

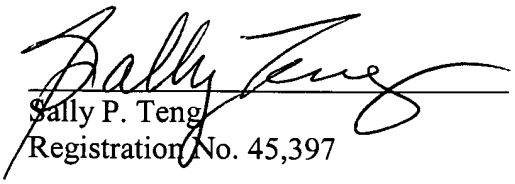
Accordingly, neither Watts *et al.* nor Podolski *et al.* provide the motivation to modify the particles to the specific size of between 10 nm to 400 nm for targeting an activated vascular site as required by the claims. There is also no motivation to modify the inventions of Watts *et al.* with the teachings of Podolski *et al.* to arrive at the claimed invention with reasonable expectation of success, since neither Watts *et al.* nor Podolski *et al* are interested in the delivery of small molecules having 10 nm to 400 nm. Thus, the cited references do not render the claimed invention obvious.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request entry of the amendments, reconsideration, and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, they are invited to telephone the undersigned at their convenience.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
Morgan, Lewis & Bockius LLP



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